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Oral Absorption and Pharmacokinetics of Rebamipide and Rebamipide Lysinate in Rats

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ABSTRACT

Rebamipide is an anti-ulcer agent exhibiting a low aqueous solubility and a poor oral bioavailability. This study was conducted to examine if the rebamipide lysinate salt form would exhibit improved solubility profiles and higher oral bioavailability compared with rebamipide free acid. Both compounds showed pH-dependent solubility profiles, with the solubility of rebamipide lysinate dramatically improved at a median pH of 5.1 (17-fold increases) over free acid, but the improvement in the solubility was not as pronounced in artificial gastric and intestinal fluids (1.4- and 1.9-fold increases, respectively). The Cl, V_{ss} and $t_{1/2}$ in rats after i.v. injection of rebamipide (0.5 mg/kg) averaged 21.0±3.2 ml/min/kg, 0.3±0.0 L/kg, and 0.4±0.1 hr, respectively. No significant difference was observed in these parameters between rebamipide and rebamipide lysinate. Despite improved solubility profiles, the absolute oral bioavailability of rebamipide lysinate was not increased (5.1 vs. 4.8%) nor did AUC (407.8 vs. 383.6 ng·hr/ml) and C_{max} (87.4 vs.77.0 ng/ml) compared with rebamipide free acid. Rebamipide lysinate, however, showed a more rapid absorption, and initial serum drug concentrations were higher than those found for rebamipide free acid.

Key Words: Rebamipide; Rebamipide lysinate; Absorption; Bioavailability; Pharmacokinetics.

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INTRODUCTION

Rebamipide {(±)-2-(4-chlorobenzoylamino)-3-[2-(1 H)quinolinon-4-yl]propionic acid, OPC-1759, CAS 11911-87-6, m.w. 370.79} is an anti-ulcer agent used in the treatment of gastric ulcers, acute gastritis, and exacerbated chronic gastritis.[1−3] It has been reported to increase the endogenous prostaglandin E2 in the gastric mucosa,[1] increase the amount of surface gastric mucus and soluble mucus in the stomach,[4] and inhibit gastric mucosal injury induced by indomethacin,[5] ethanol, acids and bases.[1,6] More recently, beneficial effects of rebamipide have been reported on experimentally induced colitis.[7]

Rebamipide is soluble in dimethylformamide, very slightly soluble in methanol and ethanol, and practically insoluble in ether and water (MUCOSTA Tablets Package Insert, Otsuka Pharmaceutical Co., Ltd., March 2000). The aqueous solubility of rebamipide has been reported to be approximately 0.0001 and 0.013% (w/v) at pH 3 and 7, respectively.[8] This drug is poorly absorbable into the systemic circulation[9] and may be classified into Class IV in Biopharmaceutics Classification System (BCS) due to its low solubility and low membrane permeability.[8] Various efforts have been made to improve the oral absorption potential of drugs with poor water solubility, i.e., by incorporating absorption enhancers and adjuvants,[10,11] and synthesizing various salt forms.[12−14] Salt formation techniques may be utilized to improve the solubility profile and oral bioavailability of rebamipide.[15]

In this study, aqueous solubility profiles of rebamipide and rebamipide lysinate were compared, and the absorption and pharmacokinetic disposition of these compounds were characterized after i.v. and oral administration to rats. Both compounds showed pH-dependent solubility profiles, with the aqueous solubility of rebamipide lysinate dramatically improved at pH 5.1 (17-fold increases) over free acid. Despite improved solubility profiles, rebamipide lysinate did not result in increased oral bioavailability, but showed a more rapid absorption compared with rebamipide free acid.

EXPERIMENTAL

Chemicals and Reagents

Ketoprofen, formic acid, phosphoric acid, dimethyl sulfoxide, polyethylene glycol 400, hydrochloride, sodium chloride, sodium hydroxide, sodium phosphate monobasic, sodium phosphate dibasic, and potassium chloride were purchased from Sigma Chem. Co. (St. Louis, MO, USA). Rebamipide and rebamipide lysinate were obtained from Jinyang Pharm. Co. (Seoul, Korea). Acetonitrile, methanol, and methyl *t*-butyl ether (All HPLC grades) were purchased from J. T. Baker (Phillipsburg, NJ, USA). Mini capsules for rodents were purchased from Shionogi Qualicaps Co. (Osaka, Japan).

Determination of Solubility

The artificial gastric fluid (pH 1.2) was prepared by dissolving 2 grams of NaCl in deionized water (Milli Q Water Purification System, Millipore, Bedford, MA, USA) and adding 7 ml of HCl (1 N) to a volume of 1 L using deionized water. The artificial intestinal fluid (pH6.8) was prepared by adding 250 ml of 0.2 M KH_2PO_4 and 118 ml of 0.2 M NaOH to 632 ml of deionized water. Rebamipide or rebamipide lysinate (50 mg as free acid) was added to the artificial gastric fluid, artificial intestinal fluid, and deionized water (10 ml each), and the solutions were maintained on a shaking water bath at 25°C with a stirring rate of 100 rpm over a 48-hr period (BS-21 Shaking Water Bath, Jeio Tech. Co., Kyeonggi, Korea). Aliquots of 0.5 ml were withdrawn at 1, 3, 6, 9, 12, 24, and 48 hr, filtered through a 0.45 mm PTFE syringe filter (Acrodisc, Waters, Milford, MA, USA), diluted to appropriate concentrations, and assayed for drug content (n=3 at each time point). Equal volumes of the blank solution were replaced after collection of each sample. Drug concentrations were determined by HPLC reported previously with slight modification.[16] The HPLC was consisted of a Shimadzu model RF-10Axl fluorescence detector, SCL-10A system controller, LC-10AT pump, SIL-10A auto-sample, and CTO-10A column oven. Chromatographic separations were achieved using a Phenomenex Luna C18 (Phenomenex, 4.6 mm × 250 mm, 5 μm, Torrance, CA, USA) and a guard column (Phenomenex Security Guard, 3.0 mm × 4.0 mm, 3.5 μm, Torrance, CA, USA). The mobile phase was a mixture of acetonitrile and 10 mM phosphate buffer (50:50 v/v) with pH adjusted to 2.5 using HCl. The flow rate of the mobile phase was maintained at 1.0 ml/min at 40°C, and the fluorescence excitation and emission wavelengths were set at 330 and 380 nm, respectively.

Animals

Male Sprague Dawley rats (7−8 weeks of age, 220−280 g) were purchased from Jeil Co. (Ansung,

Korea). The rats were placed in plastic rat cages and housed in a temperature controlled (22–25°C) animal facility with light/dark cycle of 12/12 hr and relative humidity of 50±10%. The animals had free access to standard rat diet (Daejong Co., Seoul, Korea) and water throughout the study. At least one week of acclimatization period was allowed prior to drug dosing experiments.

Intravenous Injection Study

The rats were anesthetized with i.m. injection of ketamine and xylazine (90/10 mg/kg) and cannulated with PE tubing (0.58 mm i.d. and 0.96 mm o.d., Natume Co., Tokyo, Japan) in the right femoral and left jugular vein. The animals were kept in metabolic cages until the drug dosing study was completed. After surgery, at least 2 days of recovery period was allowed prior to drug administration. Rebamipide and rebamipide lysinate were dissolved separately in a mixture of DMSO:PEG 400:water (5:55:45) and were injected immediately via the venous catheter to two groups of rats (n=5 each). The volume of the administered dosing vehicle was 2 ml/kg, and the dose was 0.5 mg/kg as rebamipide free acid for both groups of rats. Serial venous blood samples (approximately 0.3 ml each) were taken at 0, 5, 15, and 30 min, 1, 1.5, 2, and 4 hr after dosing. Equal volumes of saline were replaced after each sampling. Serum samples were harvested by centrifugation at 1,500 *g* for 5 min and were kept at −20°C until drug analysis. Urine was also collected over a 4-hr period after dosing and stored at −20°C until drug analysis.

Oral Administration Study

The rats were cannulated with PE tubing (0.58 mm i.d. and 0.96 mm o.d., Natume Co., Tokyo, Japan) in the right jugular vein, and at least a 2-day recovery period was allowed prior to drug administration. Mini capsules filled with rebamipide or rebamipide lysinate (dose 10 mg/kg as free acid) were given to rats by oral gavages (n=7–10 per group). Immediately after oral administration, approximately 0.4 ml of water was given to rats to help facilitate swallowing the capsules. The mini capsules had an external diameter cap 2.65 mm, length 8.4 mm and capacity 25 mm^3 (Shionigi Qualicaps Co., Osaka, Japan). Serial venous blood samples (approximately 0.3 ml each) were taken at 0, 5, 15, and 30 min, 1, 2, 4, 6, 8, 12, and 24 hr after drug administration. Equal volumes of saline were replaced after each sampling. Serum samples were harvested by centrifugation at 1,500 *g* for 5 min and were kept at −20°C until drug analysis.

Determination of Serum Drug Concentrations

Serum drug concentrations were determined by using a Micromass ZMD mass spectrometer (Masslynx ver. 3.5, Manchester, UK) attached to a Waters Alliance 2690 HPLC system (Waters, Milford, MA, USA). The mass spectrometric conditions were as follows: ion source ESI(−); scan type SIR; scan mass M/Z 369 (rebamipide) $[M-H]^-$, M/Z 253 (internal standard) $[M-H]^-$; desolvation temp. 280°C; source block temp. 120°C; cone voltage 20 V; capillary voltage: 2800 V; nebulizing and desolvation gas nitrogen. The analytical column was a Phenomenex Luna C18 (Phenomenex, 2.0 mm × 150 mm, 3 μm, Torrance, CA, USA) and a guard column (Phenomenex Security Guard, 2.0 mm × 4.0 mm, 3.5 μm, Torrance, CA, USA). The mobile phase was a mixture of acetonitrile:0.05 M formic acid raised from a composition of 35:65 v/v to 50:50 v/v from 3 to 9 min after each injection. The flow rate of the mobile phase was maintained at 0.2 ml/min at 40°C, and the sample injection volume was 20 μl.

Rebamipide was extracted by single liquid–liquid extraction using *t*-butyl methyl ether. Briefly, to a 100 μl of the rat serum in borosilicate tubes were added 25 μl of the internal standard solution (ketoprofen 1 μg/ml in methanol) and 500 μl of 1 N HCl and the mixture was mixed on a vortex mixer for 30 sec. The mixture was then extracted with 3 ml of *t*-butyl methyl ether on a vortex mixer for 3 min followed by centrifugation at 3,500 *g* for 10 min (Union 32R Centrifuge, Hanil Science Ind. Co., Incheon, Korea). The resulting supernatant was transferred into a fresh tube and dried at 40°C under nitrogen gas (Dry Thermo Bath MG-2100, Tokyo Rikakikai Co., Tokyo, Japan). The residue was reconstituted with 100 μl of the mobile phase on a vortex mixer for 30 sec.

Data Analysis

Obtained serum rebamipide concentration vs. time data were subjected to noncompartmental analysis by the nonlinear least squares regression program WinNonlin (Scientific Consulting Inc., Cary, NC, USA). Statistical differences were tested by the unpaired Student t-test for the solubility and pharmacokinetic parameters between rebamipide free acid and rebamipide lysinate. The significance level was set at $p<0.05$.

RESULTS AND DISCUSSION

In this study, concentrations of rebamipide in samples obtained from in vitro solubility experiments were determined by an HPLC method reported previously.[16] In addition, a highly sensitive and selective LC/MS method was developed for the determination of rebamipide in rat serum and urine samples. Rebamipide and the internal standard were well resolved, with their retention times being 5.4 and 12.5 min, respectively. The standard curve was linear over the concentration range of 2–1,000 ng/ml, with a typical correlation coefficient of r=0.9996. The extraction recovery was >83% for rebamipide over the concentration range of 2–1,000 ng/ml and 92% for the internal standard at a concentration of 250 ng/ml. The intra- and inter-day assay variabilities were <14.4% and <11.1%, respectively, over the concentra-

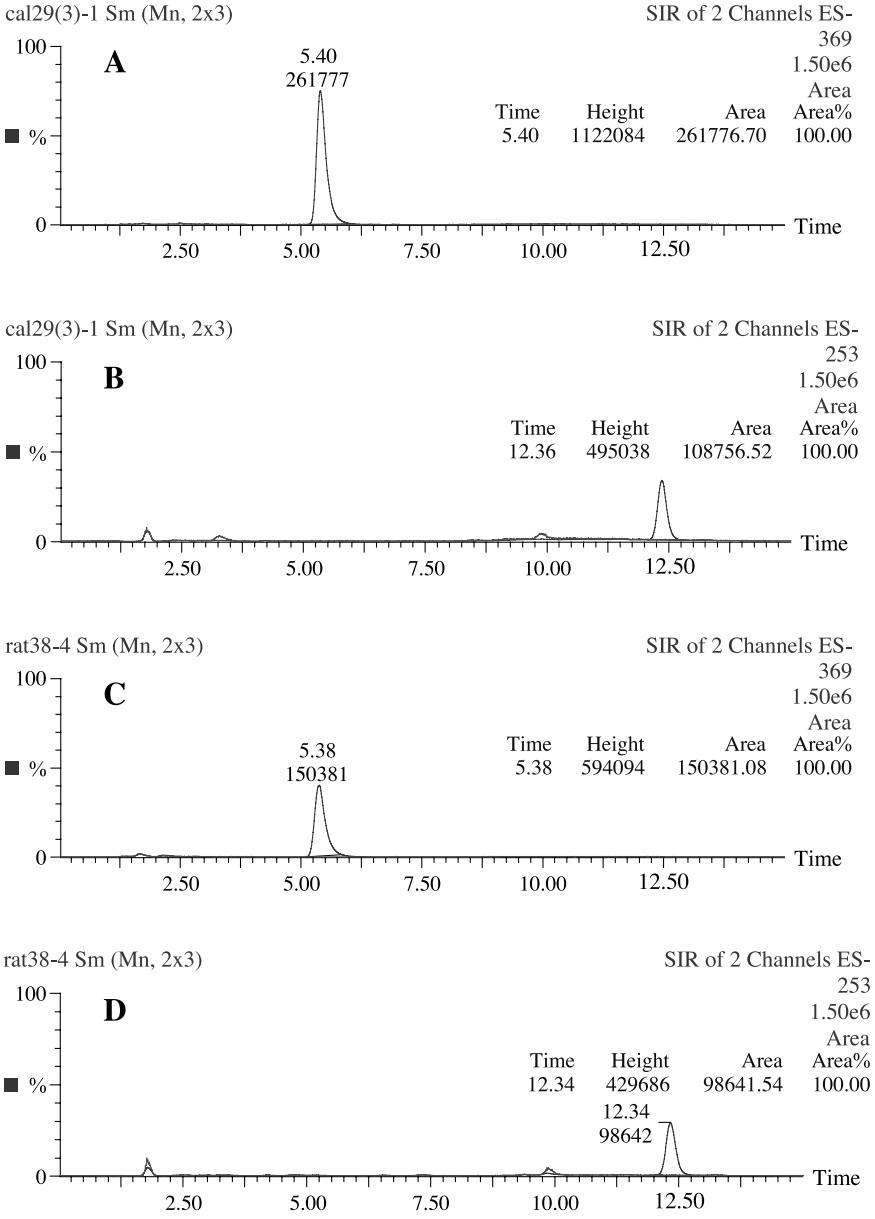

Figure 1. Representative mass chromatograms of extracted serum spiked with rebamipide (t_R=5.40 min, 1000 ng/ml) (A) and the internal standard (t_R=12.36 min, 250 ng/ml) (B), extracted serum containing rebamipide (C) (581.6 ng/ml) and the internal standard (D) obtained 15 min after a 0.5 mg/kg i.v. bolus dose.

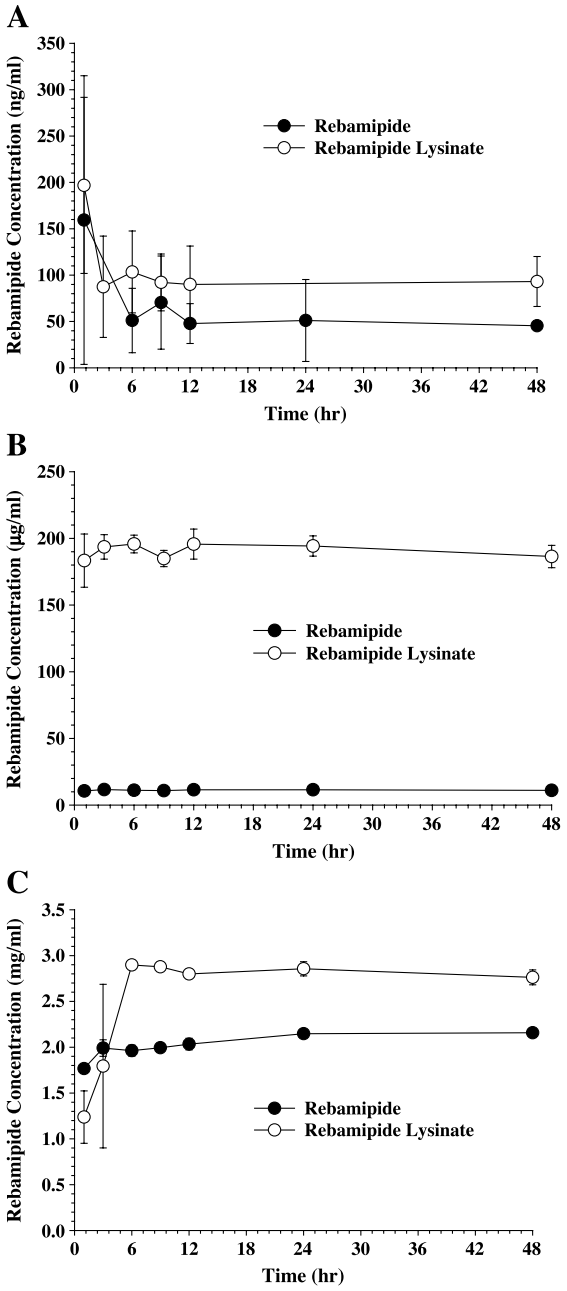

Figure 2. Average time courses of rebamipide concentration found after addition of excess amounts of rebamipide and rebamipide lysinate to artificial gastric juice (pH=1.2) (A), deionized water (pH 5.1) (B) and artificial intestinal juice (pH=6.8) (C) (n=3 each).

tion range studied (n=4 each concentration). The assay sensitivity (lower limit of quantification of 2 ng/ml using 100 μl of biological sample volumes) was higher than those reported previously (10 ng/ml).[17,18] The representative mass chromatograms of extracted serum spiked with rebamipide and internal standard and extracted serum containing rebamipide obtained 15 min after i.v. injection of rebamipide to rats (0.5 mg/kg) are shown in Fig. 1.

Both rebamipide and rebamipide lysinate showed pH-dependent aqueous solubility profiles (Fig. 2). These compounds were practically insoluble in artificial gastric fluid but were slightly soluble in artificial intestinal fluid (Table 1). Rebamipide lysinate exhibited a dramatically improved solubility at the median pH of 5.1 (17-fold increase) over the free acid, but the improvement in solubility was marginal in both the artificial gastric and intestinal fluids (1.4- and 1.9-fold increases, respectively). As an acidic compound, rebamipide is expected to be solubilized to a greater extent at increased pH conditions. This phenomenon appears evident as the solubility of rebamipide free acid is increased from 0.049 μg/ml to 11.3 μg/ml as the pH increased from 1.2 to 5.1. Similarly, the solubility of rebamipide lysinate is increased at the higher pH (11.3 vs. 191.7 μg/ml). In the simulated intestinal fluid with pH 6.8, however, rebamipide free acid may have been almost completely ionized and, as a consequence, there was no further increase in the solubility for rebamipide lysinate (Table 1).

The pharmacokinetic disposition of rebamipide and rebamipide lysinate was characterized in rats after i.v. injection (0.5 mg/kg as rebamipide free acid). The concentration-time profiles of these compounds declined in a parallel fashion (Fig. 3). Following i.v. injection of rebamipide free acid, the systemic clearance (21.0±3.2 ml/min/kg) and the steady-state volume of distribution (0.3±0.0 L/kg) were relatively low and the elimination half-life was short (0.4±0.1 hr). The majority of the administered dose (73.4±9.2%) was excreted unchanged in urine. All of these pharmacokinetic parameter values were not significantly

Table 1. Solubility of rebamipide and rebamipide lysinate determined in artificial gastric fluid (pH 1.2), deionized water (pH 5.1) and artificial intestinal fluid (pH 6.8).

Solubility (μg/ml)	Rebamipide	Rebamipide lysinate	Fold increases
Artificial gastric fluid	0.049±0.030	0.092±0.031	1.9
Deionized water	11.3±0.8	191.7±8.4	17.0
Artificial intestinal fluid	2048.0±93.2	2841.5±71.6	1.4

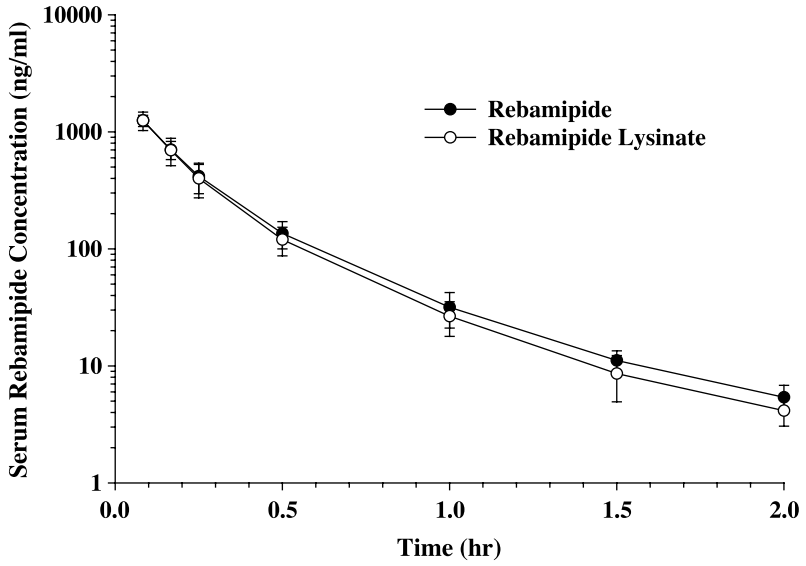

Figure 3. Average serum rebamipide concentration vs. time curves obtained after i.v. injection of rebamipide and rebamipide lysinate in rats (0.5 mg/kg as rebamipide free acid, n=5 each).

different from those obtained for rebamipide lysinate (Table 2).

In oral dosing experiments, a higher dose (10 mg/kg as rebamipide free acid) was used considering a poor oral bioavailability.[9] After oral administration of rebamipide free acid, C_{max}, T_{max} and AUC averaged 77.0±23.5 ng/ml, 2.2±2.0 hr and 383.6±109.0 ng·hr/ml, respectively (Table 3). Rebamipide was poorly absorbed into the systemic circulation, with an absolute oral bioavailability of 4.8±1.4%. The apparent terminal elimination half-life (5.4±2.2 hr) was longer than found after i.v. injection (0.4±0.1 hr), indicating a flip-flop of the absorption and elimination rate constants. This flip-flop phenomenon may be caused by the practical insolubility of rebamipide. Although rebamipide lysinate exhibited improved aqueous solubility, the absolute oral bioavailability was neither significantly increased (5.1 vs. 4.8%) nor AUC (407.8 vs. 383.6 ng.hr/ml) and C_{max} (87.4 vs.77.0 ng/ml) compared with those found for rebamipide free acid. No significant increase in oral bioavailability may have been resulted because the solubility of rebamipide lysinate was not increased from that of rebamipide free acid at the intestinal pH (Table 1). Other investigators have reported no difference in oral bioavailability between different salt forms of drugs

Table 2. Pharmacokinetic parameters of rebamipide obtained after i.v. injection of rebamipide free acid and rebamipide lysinate (0.5 mg/kg as rebamipide free acid) in rats.

Parameters	Rebamipide (n=5)	Rebamipide lysinate (n=5)
$t_{1/2}$ (hr)	0.4±0.1	0.3±0.1
Cl (ml/min/kg)	21.0±3.2	21.6±4.8
C_0 (ng/ml)	2247.8±342.1	2312.9±609.8
V_{ss} (L/kg)	0.3±0.0	0.3±0.0
AUC (ng.hr/ml)	402.6±54.3	399.9±76.9
AUMC (ng.hr^2/ml)	96.2±19.5	84.3±23.3
MRT (hr)	0.2±0.0	0.2±0.0
f_e (%)	73.4±9.2	62.4±13.3

Table 3. Pharmacokinetic parameters of rebamipide obtained after oral administration of rebamipide (n=7) and rebamipide lysinate (n=10) (10 mg/kg as rebamipide free acid) in rats.

Parameters	Rebamipide (n=7)	Rebamipide lysinate (n=10)
AUC (ng.hr/ml)	383.6±109.0	407.8±238.9
C_{max} (ng/ml)	77.0±23.5	87.4±55.4
Cl/F (ml/min/kg)	484.5±214.2	555.0±305.1
T_{max} (hr)	2.2±2.0	1.4±1.7
$t_{1/2}$ (hr)	5.4±2.2	3.8±1.4
AUMC (ng.hr^2/ml)	3,241.7±1,935.0	2,534.7±2,122.0
V_z/F (L/kg)	210.0±71.6	185.4±138.6
MRT (hr)	8.1±3.5	5.7±2.2
F (%)	4.8±1.4	5.1±3.0

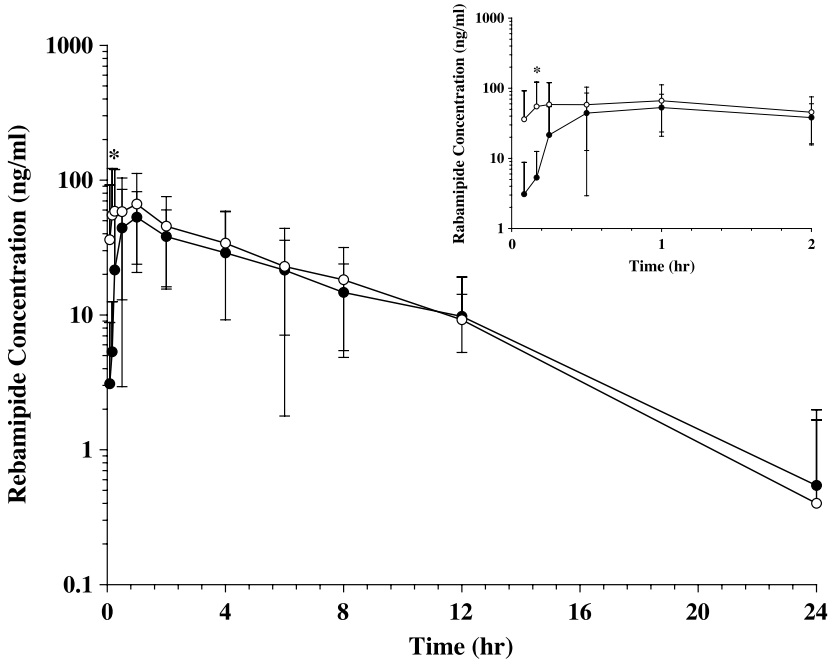

Figure 4. Average serum rebamipide concentration vs. time curves obtained after oral administration of rebamipide (●, n=7) and rebamipide lysinate (○, n=10) (10 mg/kg as rebamipide free acid).

with different solubility profiles, including quinine[19] and naftidrofuryl.[20] However, initial serum drug concentrations were significantly higher for the free acid compared with rebamipide lysinate (Fig. 4). The shorter T_{max} (1.4 vs. 2.2 hr) and apparent terminal half-life (3.8 vs. 5.4 hr) with an assumption of the flip-flop of absorption and elimination rate constants were also indicative of the relatively rapid oral absorption of rebamipide lysinate. In humans, the peak plasma concentration of rebamipide has been reported to occur 1.95–2.8 hr after oral administration.[18,21] Also, the peak concentration in human gastric mucosa and mucus is observed at 1–1.9 hr and 1–1.1 hr, respectively, after oral ingestion. Therefore, more rapid oral absorption of rebamipide lysinate found in this study may be useful in assuring a fast onset of drug action in patients with gastric ulcer and gastritis. Inter-animal variabilities in the pharmacokinetic parameters, e.g., $t_{1/2}$, Cl, V_{ss}, and AUC determined after i.v. injection of rebamipide and rebamipide lysinate were relatively small compared with those found after oral administration (Tables 2–3). It may be possible that the greater inter-animal variability after oral administration was associated with the pH-dependent solubility of these compounds along the gastrointestinal tract, especially their dramatically altered solubility at around pH 5.1. Consequently, alterations in the pH along the gastrointestinal tract, gastric emptying time and presence of food may have significant impacts on the systemic absorption of these compounds.

In conclusion, the oral absorption and pharmacokinetics of rebamipide and rebamipide lysinate were characterized in rats after i.v. and oral administration. Despite improved solubility profiles, the absolute oral bioavailability of rebamipide lysinate was not significantly increased as compared with that of rebamipide free acid. Yet, rebamipide lysinate was absorbed more rapidly, and initial serum drug concentrations were higher than those found for rebamipide free acid. The more rapid oral absorption of rebamipide lysinate may be useful in assuring a fast onset of drug action in the treatment of gastric ulcer and gastritis.

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